Treatment Results of non-Hodgkin's Lymphoma Cases in Çukurova Region of Turkey

Türkiye'nin Çukurova Bölgesinde Non-Hodgkin Lenfoma Olgularının Tedavi Sonuçları

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Abstract
Purpose: We aimed to evaluate the clinicopathological characteristics and prognostic features of non-Hodgkin lymphoma (NHL) in pediatric patients in Çukurova Region, Turkey.
Material and Methods: Histopathologically, 24 (63.2%) patients were diagnosed as Burkitt lymphoma, 12 (31.6%) patients were diagnosed as T-cell lymphoblastic lymphoma and 2 (5.2%) patients were diagnosed as diffuse large cell lymphoma. Patients were staged according to Murphy's classification in children. Treatment protocols of BFM-90 and LSA2L2 were applied to patients.
Results: While mean age of 38 patients with NHL was 75.3±41.5 months , 12 (31.6%) patients were female and 26 (68.4%) patients were male. One (2.6%) patient was evaluated as stage I, 8 (21.1%) patients were as stage II, 18 (47.4%) patients were as stage III and, 11 (28.9 %) patients were as stage IV. Overall survival for 5 years was found as 71%. When overall survival were estimated based on histopathological study, 93%, 56% and %50 were found for T-cell lymphoblastic lymphoma, Burkitt lenfoma and diffuse large cell group, respectively.
Conclusion: The prognosis of NHL cases followed by our clinic varied according to the stage and histopathological type. Although most of our cases were Burkitt or stage III-IV lymphomas, the clinical response to the treatment protocols were similar to the literature.

Key words: **Lymphoma, Non-Hodgkin; Burkitt Lymphoma.**

Özet
Amaç: Bizim amacımız, çukurova bölgesindeki NHL'lı çocuk hastalarının klinikopatolojik karakteristiklerini ve prognostic bulgularını değerlendirmektir.
Gereç ve Yöntemler: Histopatolojik olarak, 24 hasta Burkitt lenfoma, 12 hasta (%31,6) Burkitt dışı hasta ve 2 hasta ise büyük hücreli NHL idi. Hastaların evresi Murphy'nin NHL sınıflamasına göre yapıldı. Buna göre; bir hasta evre I, 8 hasta evre II, 18 hasta evre III ve 11 hasta ise evre IV idi. Hastalara BFM-90 ve LSA2L2 tedavi protokolü uygulandı.
Bulgular: NHL'lı hastaların ortalama yaşı 75,3±41,5 ay idi. Hastaların 12'si (%31,6) kız hasta ve 26'sı (%68,4) ise erkek hasta idi. 5 yıllık yaşam olasılığı %71 olarak saptandı. Histopatolojik tipine göre yaşam olasılığı; T hücreli lenfoblastik lenfomada %93, Burkitt lenfomada %56 ve Burkitt dışı büyük hücreli lenfomada ise %50 olarak saptandı.
Sonuç: Kliniğimiz tarafından takip edilen NHL'lı hastaların prognozu, histopatolojik tip ve evreye göre değişmekteydi. Bizim olgularımızın büyük kısmı Burkitt ya da evre III-IV lenfoma olmasına rağmen, tedavi protokollerine aldığımız cevap literatürle benzerdi.

Anahtar kelimeler: **Lenfoma, Non-Hodgkin; Burkitt lenfoması**

Introduction

Non-Hodgkin lymphoma (NHL) is the malignancy of lymphatic system occurred due to malignant clonal proliferation of lymphocytes. Lymphomas consist of 10-15% of the childhood cancers. It is the third common cancer type in childhood after leukemias and brain tumors. Generally 40% of lymphomas are Hodgkin's and 60% are non-Hodgkin's lymphoma. The percentage of Burkitt lymphoma and lymphoblastic lymphoma is 40-50% in NHL group. Great majority of the cases (90%) are frequently presented with abdominal mass. Cecum is the most common anatomic location for the tumor. Clinical findings of NHL in children are different. Sporadic cases of Burkitt lymphoma are often seen with abdominal location and usually presented with abdominal pain or distention, nausea, vomiting and right lower quadrant mass. Jaw involvement is observed fewer than 10% of cases of sporadic diseases (1). Various chemotherapy regimens are used in treatment of NHL. In previous studies, while survival rate ranges were approximately 54-73% between 1980 and 1990 years; they were reaching 72-82% between 1990 and 2000 years (1). These results were generally according to stage. We want to compare results treatment of NHL diagnosed by our clinic in this study.

Patients and Methods

In this study, 38 pediatric patients with non-Hodgkin's lymphoma who admitted Pediatric Oncology out-patient clinic between June 1996 and March 2004 were included. We retrospectively evaluated the patients according to age, gender, symptoms, diagnostic criteria, anatomical location, histopathological evaluation and chemotherapy. Heamatological and biochemical laboratory tests, including complete blood count, liver and renal function tests, and serological test for Ebstein-Barr virus, were performed. Histopathological diagnosis was done by 27 biopsies, 5 surgical operations, and 5 bone marrow aspiration samples. We were classified according to the Murphy's non-Hodgkin's lymphoma classification in children (1). BFM-90 treatment protocol was used both for Burkitt lymphoma and diffuse large B-cell lymphoma. LSA2L2 treatment protocol was applied for lymphoblastic lymphoma (2). We calculated overall survival (OS), event-free survival (EFS) and disease free survival (DFS) for all patients. OS was defined as the total follow up time of patients from the time of diagnosis; EFS was defined as relapse or dead from the time of diagnosis; DFS was defined as estimated length of time without relapse or disease after complete remission.

Statistical Analysis. Statistical analyses were performed by SPSS 10.01 pack program. Log rank and Kaplan Meier tests were used for the evaluation of data. $P<0.05$ was considered as statistically significant.

Results

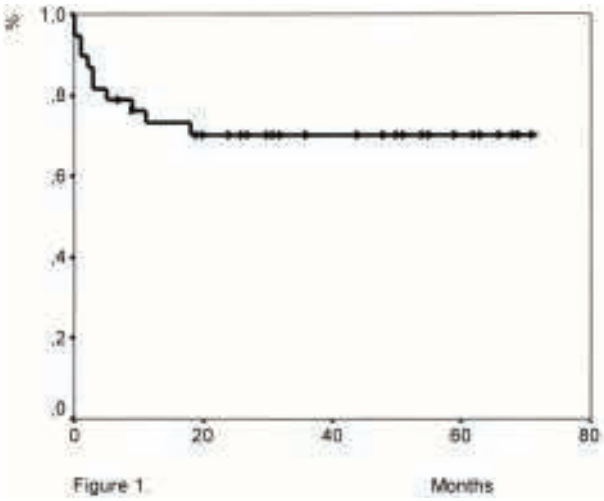
Out of all patients, 12 (31.6%) were female and 26 (68.4%) were male patients. Mean age was 75.3±41.5 (range: 33-168) months. Histopathologically, 24 (63.2%) patients had Burkitt lymphoma, 12 (31.6%) patients had lymphoblastic lymphoma and two (5.2%) patients had diffused large cell lymphoma. Ebstein-Barr virus positivity was found in three cases. Clinically, patients were divided into four stages: One (2.6%) patient as stage I, 8 (21.1%) patients as stage II, 18 (47.4%) patients as stage III and 11 (28.9 %) patients as stage IV. Central nervous system involvement was not seen in all NHL. Primary localization was in abdomen (n=31; 81.6%). Others were thorax (n=4; 10.5%), nasopharynx (n=2; 5.3%) and cervical region (n=1; 2.6%). Three patients had ascites. LDH levels were high than 500 U in 33 patients (86.8%), and high than 1000 U in 14 patients (38.9%). BFM-90 treatment protocol was applied to 26 of the cases (68.4%) and LSA2L2 for 12 cases (31.6%). OS for 5 years was detected as 71%. The prognosis of NHL cases being followed by our clinic varied based on the stage and histopathological subtype of disease. Median follow time was 30.5 (1-71)±24.5 months, and OS, EFS and DFS were estimated as 70% for 5 years. All of patients were followed until 72 months (Figure 1).

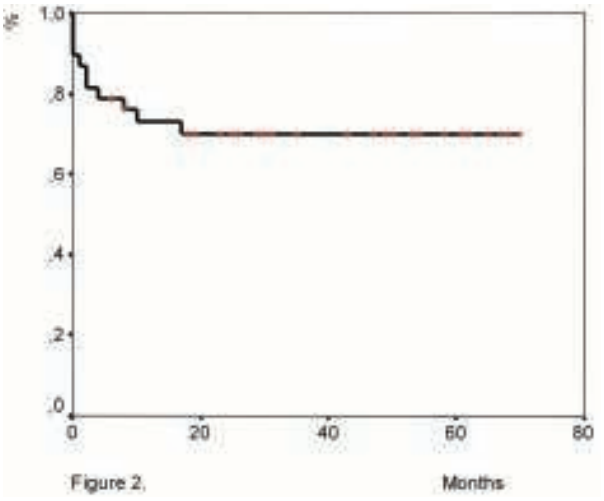
OS analyzed for gender was not statistically significant different ($p>0.05$) (Table I). According to the age, both 3 and 5-years of OS were 80% in children who are older than 4 years. But children who were younger than 4 years had 52% for 3 and 5-year of OS. Statistically significant difference was detected between the two groups ($p=0.047$). Others were shown in the Table I.

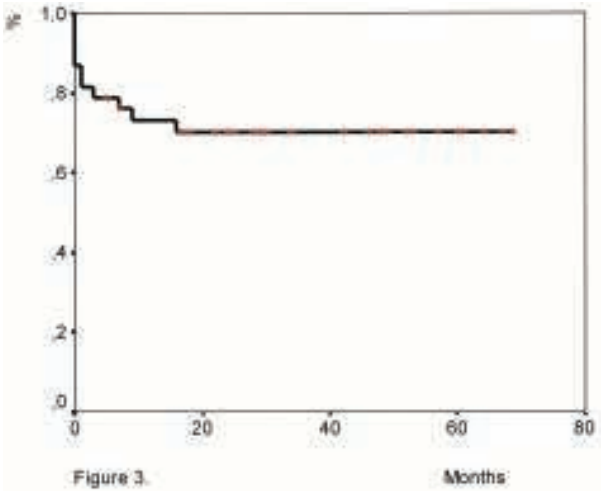
Table I. Factors Affecting Overall Survival (Kaplan-Meier Test).

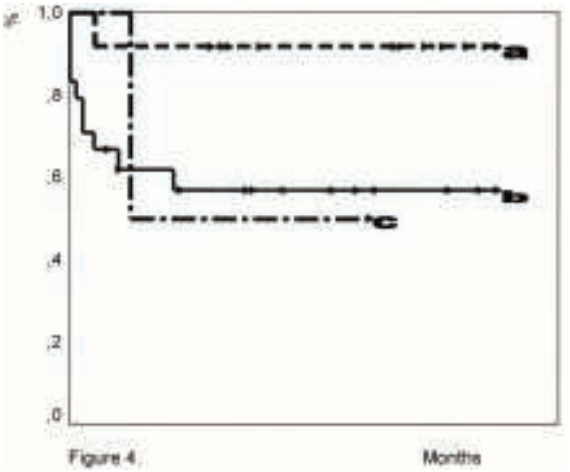
	n	OS (3 years)%	OS (5 years)%	Log rank p value
Gender				
Female	12	75	75	
Male	26	68	68	0.80
Age				
>4 years	25	80	80	0.047
≤4 years	13	52	52	
Diagnosis				
Lymphoblastic lymphoma	12	93	93	
Burkitt lymphoma	24	56	56	0.022
Diffuse large cell lymphoma	2	50	50	
Bone marrow involvement				
Positive	11	46	46	
Negative	27	78	78	0.035
Bone marrow involvoment in Burkitt lymphoma				
Positive	7	15	15	
Negative	17	75	75	0.002
Pleural effusion				
Positive	7	72	72	
Negative	31	70	70	0.83
Stage				
I-III	20	76	76	0.29
IV	18	62	62	
Lymphadenopathy				
Positive	26	64	64	0.28
Negative	12	83	83	
SGOT				
≥45 IU/ml	12	66	66	
<45 IU/ml	26	77	77	0.39
SGPT				
≥45 IU/ml	7	57	57	
<45 IU/ml	31	78	78	0.26
LDH				
≥1000 IU/ml	14	64	64	
<1000 IU/ml	24	72	72	0.58
White blood cells count				
≥10000 /mm^3	11	82.5	82.5	
<10000 /mm^3	29	67.5	67.5	0.51

Note: statistical tests were not applied in less than seven cases for all group.









Figures: Fig 1; Overall survival, fig 2; Event free survival, fig 3; Disease free survival, fig 4; a: Lymphoblastic lymphoma, b: Burrkitt lymphoma, c: Diffuse large cell lymphoma according to Kaplan Meier Curves For Overall Survival, respectively.

Discussion

Childhood NHL is classified into four major subtypes, Burkitt's lymphoma, lymphoblastic lymphoma, diffused Large Bcell lymphoma and anaplastic large cell lymphoma (1, 3). Multiagent chemotherapy is superior to monotherapy (4-10). Most of the oncologists use different chemotherapy regimens for B and T-cell lymphomas. The success rate of radiotherapy and surgical treatment added to monotherapy is reported as 18% (11). The cure rate with combined therapy or radiotherapy added to combined therapy might be 90% for a few years (12,13). However radiotherapy has no place in early treatment, it is significantly related to toxic effects in cases treated with combined agent therapy (1). Surgical operations were performed only in five patients, and radiotherapy was used only in two patients in our clinic.

Clinical findings of NHL in children could be different. Sporadic cases of Burkitt lymphoma is often in the abdomen and these are usually present with abdominal pain or distention, nausea and vomiting and right lower quadrant mass. Jaw involvement is observed fewer than 10% of cases of sporadic disease. Sporadic cases are seen

worldwide. It is usually detected in the abdomen and mediastinum, but less in the bone-marrow, nasopharynx and ovary. The peak age of NHL is 11 years. Epstein-Barr virus is presented in 15–20% of cases (1,14). In the this study, we found abdomen localization in most of the case. Besides, Ebstein-Barr virus positivity was found in three cases (7.9%) in our study.

Madani and co-workers (15) applied LMB-89 protocol for 95 patients and reported 5-years non-relapsed OS as 56%. According to stages, OS was 100%, 84%, 52% and 38% in stage I, II, III and IV, respectively. Wessels et al (16), applied LSA2L2 protocol to T-cell NHL cases and detected EFS rate as 70% for all groups. LMB-89 protocol was given for B-cell NHL cases (most of them were stage III or IV) and EFS was reported 25%. 87% of EFS rate was found after applying of LMB-96 protocol. In another study, full remission was achieved in 87% of NHL patients being treated in between 1979-2003. They reported the EFS as 65% in NHL cases (17). Laver et al (18), reported 4-year OS and EFS rates of NHL being treated in between 1994-2000 as 71.8% and 88.1%, respectively. Acquatella out co-workers (19), achieved to get full remission in 73% of B-cell NHL whom applied LMB-89 protocol. Two years OS and EFS were 82% and 75% respectively. EFS rates were reported 94% in stage I, 97% in stage II, 83% in stage III and 79% in stage IV by Marky out co-workers (20). According to the histological subtypes, the rates of EFS were found as 87% in B-cell NHL, 81% in pre-B cell NHL and 79% in T-cell NHL.

The results of our study were similar to that of literature. OS and EFS were 73%, 71% and 71% at 12,18 and 24 months, respectively. All of them follow up to 72 months. DFS was 73% for 12 months, 70% for 18 months and continued until 72 months (fig. 1-3). According to histological subtypes of NHL, both 3 and 5- year of OS were 93%, 56% and 50% in lymphoblastic lymphoma; Burkitt lymphoma and diffuse large B-cell lymphoma, respectively. Also correlation findings of EFS were similar to OS results in terms of histological subtypes of NHL. Unfortunately, poor prognosis of Burkitt and diffuse large B cell lymphoma was seen in our study.

Lactate is made up by the result of anaerobic glycolysis in cells and causes acidosis (21). Cancer cells do not live in acidic pH. Lactate is converted to pyruvate by LDH enzyme. Pyruvate is used for energy in the cells (both cancer cells and normal cells). Thus, blood pH does not change and lactate is consumed by cancer cells. Serum LDH is an important marker which is detected for following the progress of NHL. If the LDH level increases, for example 1000 IU/ml or higher, this result may likely reveal severe or progressing of disease and poor outcome (22). LDH levels were found high than 500 IU/ml in 33 patients (86,8%), and high than 1000 IU/ml in 14 patients (38,9%). Similarly, when we found plasma LDH levels 1000 IU/ml and below in our patients, the rate of OS was higher than other group who had LDH higher than 1000 IU/ml (Table I).

In conclusion, the prognosis of NHL cases followed by our clinic varied due to the stage, plasma LDH levels and histopathological subtype. While OS and EFS were seen as 71%, DFS was 70%. Response to treatment protocols were similar to that of literature although most of our cases had Burkitt or advanced stage lymphomas.

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